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=> d his

     (FILE 'HOME' ENTERED AT 09:14:43 ON 24 JUN 2007)

     FILE 'REGISTRY' ENTERED AT 09:14:54 ON 24 JUN 2007
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L2          13 S L1 SSS SAM
L3         254 S L1 SSS FULL
L4             STRUCTURE UPLOADED
L5           9 S L4 SSS SAM
L6         122 S L4 SSS FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 09:20:01 ON 24 JUN 2007
L7         979 S L3
L8          30 S L6
L9          12 S L7 AND APOPTOSIS
L10          0 S L7 AND CYTOSTATICS
L11          1 S L7 AND AFTER CHEMO?
L12          0 S L7 AND CHEMO? (P) CYCLE?
L13          0 S L7 AND POST CHEMO?
L14          0 S L7 AND POST (P) CHEMO?
L15          3 S L7 AND RECOVER? (P) CHEMO?
L16         89 S L7 AND CHEMO?
L17          8 S L16 AND SYNERGI?
L18         81 S L16 NOT L17
L19          3 S L18 AND SIDE EFFECT?
L20         30 S L8 NOT L19
L21         78 S L18 NOT L19
L22         15 S L21 AND REDU?
L23         63 S L21 NOT L22
L24         24 S L23 AND EFFECT?
L25          2 S L6 AND APOPTOSIS
L26          0 S L6 AND CYOSTAT?
L27          0 S L6 AND CHEMO (P) CYCLE?
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L30          0 S L6 AND RECOV? (P) CHEMO?
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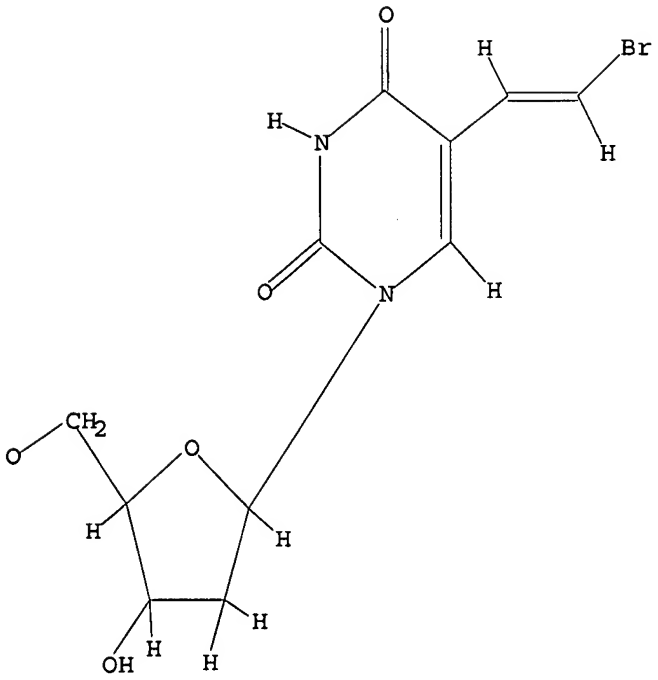

Structure attributes must be viewed using STN Express query preparation.

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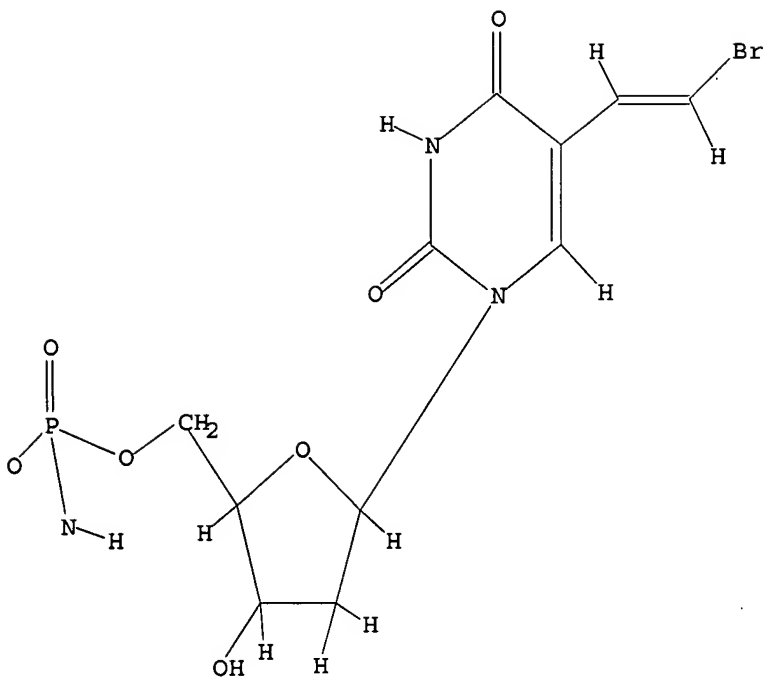


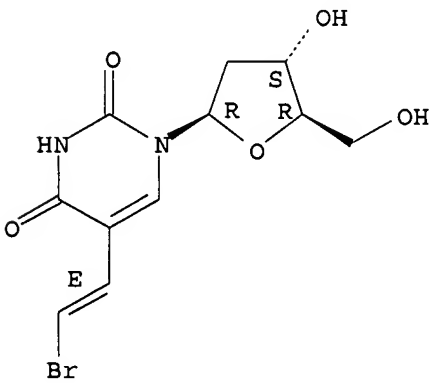
Structure attributes must be viewed using STN Express query preparation.

L9 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:780065 CAPLUS
DOCUMENT NUMBER: 140:104666
TITLE: Inhibition of Induced Chemoresistance by Cotreatment with (E)-5-(2-Bromovinyl)-2'-Deoxyuridine (RP101)
AUTHOR(S): Fahrig, Rudolf; Heinrich, Joerg-Christian; Nickel, Bernd; Wilfert, Falk; Leisser, Christina; Krupitza, Georg; Praha, Christian; Sonntag, Denise; Fiedler, Beate; Scherthan, Harry; Ernst, Heinrich
CORPORATE SOURCE: RESprotect, Dresden, D-01307, Germany
SOURCE: Cancer Research (2003), 63(18), 5745-5753
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB VInduced chemoresistance leads to the reduction of apoptotic responses. Although several drugs are in development that circumvent or decrease existing chemoresistance, none has the potential to prevent or reduce its induction. Here, we present data from a drug that could perhaps fill this gap. Cotreatment of chemotherapy with (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU, RP101) prevented the decrease of apoptotic effects during the course of chemotherapy and reduced nonspecific toxicity. Amplification of chemoresistance genes (Mdr1 and Dhfr) and overexpression of gene products involved in proliferation (DDX1) or DNA repair (UBE2N and APEX) were inhibited, whereas activity of NAD(P)H: quinone oxidoreductase 1 (NQO1) was enhanced. During recovery, when treatment was with BVDU only, microfilamental proteins were up-regulated, and proteins involved in ATP generation or cell survival (STAT3 and JUN-D) were down-regulated. That way, in three different rat tumor models, the antitumor efficiency of chemotherapy was optimized, and toxic side effects were reduced. Because of these beneficial properties of BVDU, a clin. pilot Phase I/II study with five human tumor entities has been started at the University of Dresden (Dresden, Germany). So far, no unwanted side effects have been observed

IT 69304-47-8, BVDU
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of chemoresistance by cotreatment with (E)-5-(2-bromovinyl)-2'-deoxyuridine)
RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



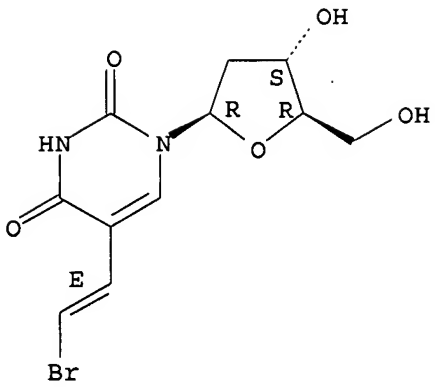
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:741595 CAPLUS
DOCUMENT NUMBER: 140:104511
TITLE: Comparison of HSV-1 thymidine kinase-dependent and -independent inhibition of replication-competent adenoviral vectors by a panel of drugs
AUTHOR(S): Wildner, Oliver; Hoffmann, Dennis; Jogler, Christian; Ueberla, Klaus
CORPORATE SOURCE: Bldg. MA, Abteilung fuer Molekulare und Medizinische Virologie, Ruhr-Universitaet Bochum, Bochum, D-44801, Germany
SOURCE: Cancer Gene Therapy (2003), 10(10), 791-802
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Replication-competent adenoviral vectors hold the promise to be more efficient gene delivery vehicles than their replication-deficient counterparts, but they are also associated with a higher risk for adverse effects, especially in light of the fact that there is no established effective therapy for serious, disseminated adenovirus infection. To assess whether the therapeutic options to inhibit adenoviral replication can be enhanced by expressing a suicide gene, we examined the antiadenoviral effects of 15 drugs against wild-type adenovirus type 5 (Ad5) and an Ad5-based replication-competent vector expressing herpes simplex virus-1 thymidine kinase (HSV-tk) (Ad.OW34) using a real-time polymerase chain reaction -based assay and flow cytometry. Ad5 and Ad.OW34 were highly susceptible to the fluorinated pyrimidine analogs 5-fluoro-2'-deoxyuridine (FUdR), 5-fluorouridine (FUR), and trifluorothymidine (TFT), with a mean 50% inhibitory concentration (IC50) ranging from 0.12 to 0.32 μM. The mean IC50 of ribavirin and cidofovir (CDV) for Ad5, the most frequently used drugs to treat adenovirus disease, was 6.87 and 3.19 μM, resp. In contrast to Ad5, the Ad.OW34 vector was susceptible to (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVdU, IC50 0.09 μM), ganciclovir (GCV, IC50 0.19 μM), and acyclovir (ACV, IC50 32.04 μM). Addnl., we demonstrated in an animal model that Ad.OW34 vector replication can be inhibited significantly by GCV, CDV, and TFT by 35.2, 7.7, and 3.7-fold, resp., compared to untreated animals. The observed antiadenoviral effects were primarily not through cell killing, since the in vitro 50% cytotoxic concns. (CC50) were more than 1000 times higher than the antiadenoviral IC50 of the drugs examined, even in cells stably expressing HSV-tk. Since for HSV-tk-dependent inhibition of adenoviral vectors, stability of HSV-tk expression is crucial, we examined Ad.OW34 vector stability, by passaging the vector 10 times serially in the presence of 10 μM GCV. The HSV-tk/GCV system neither changed the susceptibility of Ad.OW34 to GCV significantly nor detectable vector rearrangements occurred, suggesting that the system might be suitable as a fail-safe mechanism to stop adenoviral vector replication.

IT 69304-47-8, BVdU
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of replication competent adenoviral vectors by a panel of drugs)
RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD: ALL CITATIONS AVAILABLE IN THE RE FORMAT

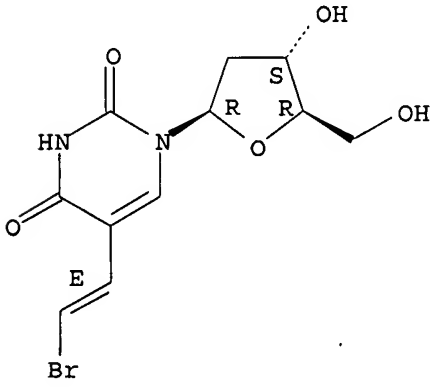
L9 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:78938 CAPLUS
DOCUMENT NUMBER: 139:30226
TITLE: Apoptosis induced by (E)-5-(2-bromovinyl)-2'-deoxyuridine in varicella zoster virus thymidine kinase-expressing cells is driven by activation of c-Jun/activator protein-1 and Fas ligand/caspase-8
AUTHOR(S): Tomicic, Maja T.; Friedrichs, Claudia; Christmann, Markus; Wutzler, Peter; Thust, Rudolf; Kaina, Bernd
CORPORATE SOURCE: Institute of Toxicology, Medical Faculty, University of Mainz, Mainz, Germany
SOURCE: Molecular Pharmacology (2003), 63(2), 439-449
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mol. mode of cell killing by the antiviral drug (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) was studied in Chinese hamster ovary (CHO) cells stably transfected with the thymidine kinase gene (tk) of varicella zoster virus (CHO-VZVtk). The colony-forming ability of the cells was reduced to <1% at a concentration of .apprx.1 μM BVDU, whereas for nontransfected cells or cells transfected with tk gene of herpes simplex virus type 1 (CHO-HSVtk), a 1000-fold higher dose was required to achieve the same response. BVDU inhibited thymidylate synthase in CHO-VZVtk but not in CHO-HSVtk and control cells. On the other hand, the drug was incorporated into DNA of VZVtk- and HSVtk-expressing cells to nearly equal amts. Because coexposure of CHO-VZVtk cells to exogenous thymidine protected them from BVDU-induced cell killing, the cells obviously die because of thymidine depletion. At highly cytotoxic BVDU doses (50 μM) and longer exposure times (24-48 h), VZVtk cells were blocked to some extent in S and G2/M phase and underwent apoptosis (48-72 h). Not only apoptosis but also necrosis was induced. The findings also show that the drug causes the induction of c-Jun and the activation of activator protein-1 resulting in increased level of Fas ligand (FasL) and caspase-8/-3 activation. Bid and poly(ADP-ribose) polymerase were cleaved by caspases. Expression of Bax increased, whereas Bcl-2/Bcl-xL remained unchanged. Transfection of dominant-neg. Fas-associated death domain and inhibition of caspase-8 by N-benzyloxycarbonyl-IETD-fluoromethyl ketone strongly abrogated BVDU-induced apoptosis, indicating Fas/FasL to be crucially involved. Thus, BVDU-triggered apoptosis differs significantly from that induced by ganciclovir, which induces in the same cellular background the mitochondrial damage pathway.

IT 69304-47-8, BVDU

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
((E)-5-(2-bromovinyl)-2'-deoxyuridine induces apoptosis of varicella zoster virus thymidine kinase-expressing cells via c-Jun/AP-1 and Fas/caspase pathways)
RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

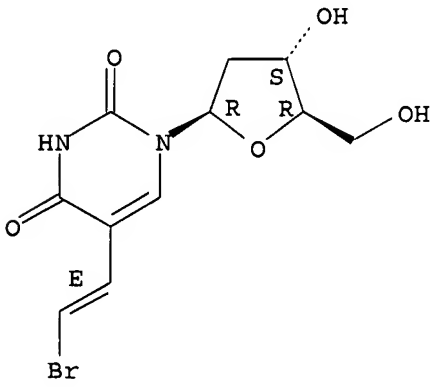
L9 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:871901 CAPLUS
DOCUMENT NUMBER: 134:172776
TITLE: The role of cellular- and prodrug-associated factors in the bystander effect induced by the Varicella zoster and Herpes simplex viral thymidine kinases in suicide gene therapy
AUTHOR(S): Grignet-Debrus, Christine; Cool, Vincent; Baudson, Nathalie; Velu, Thierry; Calberg-Bacq, Claire-Michelle
CORPORATE SOURCE: Laboratory of Fundamental Virology and Immunology, Institute of Pathology, B23, University of Liege, Liege, 4000, Belg.
SOURCE: Cancer Gene Therapy (2000), 7(11), 1456-1468
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To investigate the factors influencing the bystander effect, a key element in the efficacy of suicide gene therapy against cancer, we compared the effect triggered by four extremely efficient gene/prodrug combinations, i.e., VZVtk/BVDU, the thymidine kinase of Varicella zoster virus associated with (E)-5-(2-bromovinyl)-2'-deoxyuridine; VZVtk/BVaraU, the same enzyme associated with (E)-5-(2-bromovinyl)-1-β-D-arabinofuranosyluracil; HSVtk/BVDU, the association of the Herpes simplex virus thymidine kinase with BVDU; and the classical HSVtk/GCV (ganciclovir) paradigm. The cells used, the human MDA-MB-435 breast cancer, and the rat 9L glioblastoma lines were equally sensitive in vitro to these four assocns. In both cell types, the combinations involving pyrimidine analogs (BVDU, BVaraU) displayed a smaller bystander killing than the combination involving the purine analog (GCV). In addition, the bystander effect induced by all the tk/prodrug systems was reduced in MDA-MB-435 cells in comparison to 9L cells; albeit, the viral kinases were produced at a higher level in the breast cancer cells. All systems induced apoptotic death in the two cell types, but the MDA-MB-435 cells, deprived of connexin 43, were noncommunicating in

striking contrast with the 9L cells. That functional gap junctions have to be increased in order to improve the breast cancer cell response to suicide gene therapy was demonstrated by transducing the Cx43 gene: this modification enhanced the bystander effect associated in vitro with GCV treatment and, by itself, decreased the tumorigenicity of the untreated cells. However, the noncommunicating MDA-MB-435 cells triggered a significant bystander effect both in vitro and in vivo with the HSVtk/GCV system, showing that communication through gap junctions is not the only mechanism involved.

IT 69304-47-8, BVDU
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(role of cellular- and prodrug-associated factors in bystander effect induced by Varicella zoster and Herpes simplex viral thymidine kinases in suicide gene therapy)

RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:449761 CAPLUS
DOCUMENT NUMBER: 131:295152
TITLE: Selective activity of various antiviral compounds against HHV-7 infection
AUTHOR(S): Zhang, Ying; Schols, Dominique; De Clercq, Erik
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Antiviral Research (1999), 43(1), 23-35
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

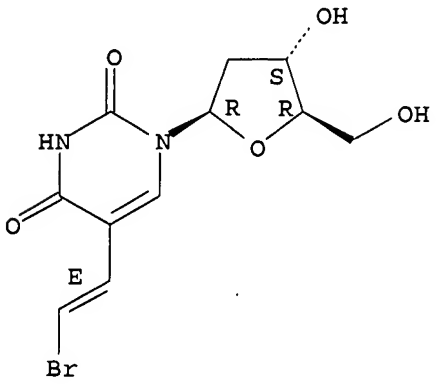
AB Human herpesvirus virus type 7 (HHV-7) is a T-lymphotropic herpesvirus which uses the CD4 receptor as main receptor to infect its target cells. Measuring the decrease of CD4 expression during HHV-7 infection is a convenient and accurate method to monitor the efficacy of antiviral agents against HHV-7 infection. Different classes of compds., such as heparin, pentosan polysulfate (PS), dextran sulfate (DS), aurintricarboxylic acid (ATA), phosphonoformic acid (PFA), 9-(2-phosphonylmethoxyethyl)adenine (PMEA), 2-amino-7-[(1,3-dihydroxy-2-propoxy) methyl]purine (S2242), polyvinylalc. sulfate (PVAS) and the co-polymer of vinylalc. sulfate with acrylic acid (PAVAS), acyclovir (ACV), ganciclovir (GCV), penciclovir

(PCV), brivudin (BVDU), cidofovir (HPMPC), lobucavir, (R)-9-[4-hydroxy-2-[(hydroxymethyl)butyl]guanine] (H2G), (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA) and sorivudine (BVaraU), were evaluated for their anti-HHV-7 activity in the SupT1 T cell line and in purified CD4+ T lymphocytes. Antiviral activity was monitored by inhibition of: (i) CD4 expression down-regulation; (ii) giant cell formation and (iii) apoptosis induction. In general, PS, DS, PVAS, PAVAS, ATA, PFA, PMEA, S2242, lobucavir and HPMPC had comparable anti-HHV-7 activity in the two cell lines, irresp. of the parameters followed to monitor antiviral activity. One of the exceptions was heparin which had an IC50 of 9.6 μg/mL in SupT1 cells and >250 μg/mL in CD4+ T lymphocytes. The compds. PCV, GCV, H2G and PMPA showed some activity in CD4+ T lymphocytes, but not in SupT1 cells. ACV, BVDU and BVaraU did not show activity in either cell system. None of the chemokines tested, such as platelet factor-4 (PF-4), eotaxin, stromal cell-derived factor 1α (SDF-1α) and RANTES, had detectable activity against HHV-7. In contrast, the HIV-1 envelope glycoprotein, gp120, and the two anti-CD4 mAbs, 13B8-2 and OKT4, were clearly active against HHV-7 infection.

IT 69304-47-8, Bvdu
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective activity of various antiviral compds. against HHV-7 infection)

RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2006664897 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17001178
TITLE: RP101 improves the efficacy of chemotherapy in pancreas carcinoma cell lines and pancreatic cancer patients.
AUTHOR: Fahrig Rudolf; Quietzsch Detlef; Heinrich Jorg-Christian; Heinemann Volker; Boeck Stefan; Schmid Roland M; Praha Christian; Liebert Andreas; Sonntag Denise; Krupitza Georg; Hanel Mathias
CORPORATE SOURCE: RESprotect, Dresden Germany.. fahrig@resprotect.de
SOURCE: Anti-cancer drugs, (2006 Oct) Vol. 17, No. 9, pp. 1045-56. Journal code: 9100823. ISSN: 0959-4973.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200612
ENTRY DATE: Entered STN: 15 Nov 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 4 Dec 2006

AB RP101 [(E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)], which supports apoptosis and prevents the acquisition of chemoresistance, was tested in cultured human pancreatic tumor cells. RP101 downregulated uridine phosphorylase, a marker of poor prognosis, and APEX1, which is involved in DNA repair, and repressed Stat3 and its target vascular endothelial growth factor. Furthermore, RP101 activated antitumor immunity as demonstrated by enhanced cytolytic activity of NK-92 natural killer cells. This was concomitant with an enhanced expression of lymphotoxins alpha and beta, natural killer cell transcript 4, tumor necrosis factor LIGHT/TNFSF-14, and intercellular adhesion molecule-1 in pancreas carcinoma cells. These results encouraged us to investigate the effect of RP101 in pancreas cancer patients. Here, we present data from two RP101 combination therapy schemes. In a first pilot study, 13 patients in stage III and VI of the disease were treated with gemcitabine +cisplatin+RP101. RP101 co-treatment enhanced remissions, survival and time to progression. Seventy-seven percent of the patients lived or have lived longer than 1 year, and 23% have lived more than 2 years. Median survival was 447 days, time to progression 280 days and the response rate 33%. A second study with 21 patients in similar stages of disease, treated with RP101+gemcitabine alone, confirmed the results of the pilot study. Eighty-three percent of the presently evaluable patients live or lived 0.5 years or longer and 33% 1 year or longer. Considering both studies, the tumor control was 94%. The data indicate that acquisition of chemoresistance was prevented and the antitumor efficacy of standard chemotherapy was improved. To our knowledge, RP101 co-treatment is more efficient than any other regimen published.

L9 ANSWER 12 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2003059293 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12527816
TITLE: Apoptosis induced by (E)-5-(2-bromovinyl)-2'-deoxyuridine in varicella zoster virus thymidine kinase-expressing cells is driven by activation of c-Jun/activator protein-1 and Fas ligand/caspase-8.
AUTHOR: Tomicic Maja T; Friedrichs Claudia; Christmann Markus; Wutzler Peter; Thust Rudolf; Kaina Bernd
CORPORATE SOURCE: Institute of Toxicology, Medical Faculty, University of Mainz, Mainz, Germany.
SOURCE: Molecular pharmacology, (2003 Feb) Vol. 63, No. 2, pp. 439-49.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 7 Feb 2003
Last Updated on STN: 22 Feb 2003
Entered Medline: 21 Feb 2003

AB The molecular mode of cell killing by the antiviral drug (E)-5-(2-bromovinyl-2'-deoxyuridine (BVDU) was studied in Chinese hamster ovary (CHO) cells stably transfected with the thymidine kinase gene (tk) of varicella zoster virus (CHO-VZVtk). The colony-forming ability of the cells was reduced to <1% at a concentration of approximately 1 microM BVDU, whereas for nontransfected cells or cells transfected with tk gene of herpes simplex virus type 1 (CHO-HSVtk), a 1000-fold higher dose was required to achieve the same response. BVDU inhibited thymidylate

synthase in CHO-VZVtk but not in CHO-HSVtk and control cells. On the other hand, the drug was incorporated into DNA of VZVtk- and HSVtk-expressing cells to nearly equal amounts. Because coexposure of CHO-VZVtk cells to exogenous thymidine protected them from BVDU-induced cell killing, the cells obviously die because of thymidine depletion. At highly cytotoxic BVDU doses (50 microM) and longer exposure times (24-48 h), VZVtk cells were blocked to some extent in S and G2/M phase and underwent apoptosis (48-72 h). Not only apoptosis but also necrosis was induced. The findings also show that the drug causes the induction of c-Jun and the activation of activator protein-1 resulting in increased level of Fas ligand (FasL) and caspase-8/-3 activation. Bid and poly(ADP-ribose) polymerase were cleaved by caspases. Expression of Bax increased, whereas Bcl-2/Bcl-x(L) remained unchanged. Transfection of dominant-negative Fas-associated death domain and inhibition of caspase-8 by N-benzyloxycarbonyl-IETD-fluoromethyl ketone strongly abrogated BVDU-induced apoptosis, indicating Fas/FasL to be crucially involved. Thus, BVDU-triggered apoptosis differs significantly from that induced by ganciclovir, which induces in the same cellular background the mitochondrial damage pathway.

L9 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:409543 CAPLUS
DOCUMENT NUMBER: 142:457053
TITLE: Human protein IAP (inhibitor of apoptosis protein) nucleobase oligomers, including dsRNA, shRNA, and siRNA, and their use for enhancing apoptosis in cancer therapy
INVENTOR(S): Lacasse, Eric; McManus, Daniel
PATENT ASSIGNEE(S): Aegera Therapeutics, Inc., Can.
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005042558	A1	20050512	WO 2004-CA1902		20041029
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
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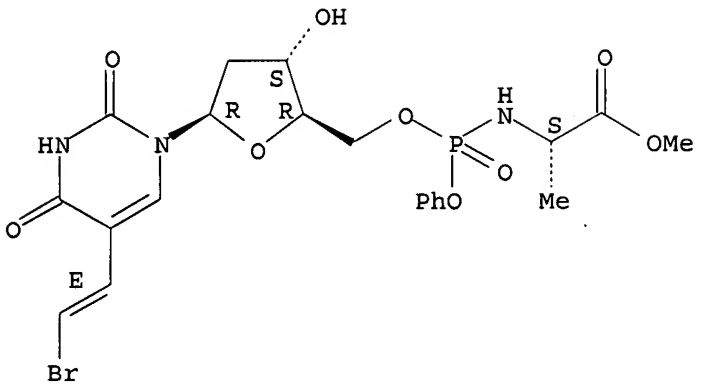
CA 2542904	A1	20050512	CA 2004-2542904		20041029
EP 1682565	A1	20060726	EP 2004-789809		20041029
R: DE, FR, GB					
JP 2007510408	T	20070426	JP 2006-537024		20041029
PRIORITY APPLN. INFO.:			US 2003-516192P	P	20031030
			WO 2004-CA1902	W	20041029

AB The invention provides nucleobase oligomers and oligonucleotide duplexes that inhibit expression of an IAP (inhibitor of apoptosis protein), and methods for using them to induce apoptosis in a cell. Specifically, the invention provides nucleic acid sequences for siRNAs and shRNAs that target human XIAP, HIAP-1 or HIAP-2 genes. The nucleobase oligomers and oligomer complexes of the present invention may also be used to form pharmaceutical compns. The invention also features methods for enhancing apoptosis in a cell by administering a nucleobase oligomer or oligomer complex of the invention in combination with a chemotherapeutic or chemosensitizing agent. RNAi sequences and vectors producing shRNA (short hairpin RNA) were transfected into HeLa cells and evaluated for their effect on XIAP, cIAP-1, or cIAP-2 protein levels. XIAP protein could also be reduced by RNAi clones in transfected breast cancer cell line MDA-MB-231. In addition, cell survival was reduced in XIAP RNAi transfected breast cancer cell line after the transfected cells were treated with TRAIL (tumor necrosis factor-related apoptosis inducing ligand).
IT 232925-18-7, Thymectacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(human protein IAP (inhibitor of apoptosis protein) nucleobase oligomers, including dsRNA, shRNA, and siRNA, and their use for enhancing apoptosis in cancer therapy)
RN 232925-18-7 CAPLUS
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L9 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:409357 CAPLUS
DOCUMENT NUMBER: 142:457052
TITLE: Sequences of antisense IAP (inhibitor of apoptosis protein) oligomers and their use for treatment of proliferative diseases with a chemotherapeutic agent
INVENTOR(S): Lacasse, Eric; McManus, Daniel; Durkin, Jon P.
PATENT ASSIGNEE(S): Aegera Therapeutics, Inc., Can.
SOURCE: PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005042030	A1	20050512	WO 2004-CA1900	20041029
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005119217	A1	20050602	US 2004-975790	20041028
AU 2004284855	A1	20050512	AU 2004-284855	20041029
CA 2542884	A1	20050512	CA 2004-2542884	20041029
EP 1691842	A1	20060823	EP 2004-789807	20041029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004015779	A	20061226	BR 2004-15779	20041029
CN 1901939	A	20070124	CN 2004-80039601	20041029
JP 2007509861	T	20070419	JP 2006-537023	20041029
IN 2006MN00614	A	20070420	IN 2006-MN614	20060526
NO 2006002420	A	20060731	NO 2006-2420	20060529
PRIORITY APPLN. INFO.:			US 2003-516263P P	20031030
			WO 2004-CA1900 W	20041029

AB The invention claims the use of an antisense oligomer to human XIAP, IAP-1

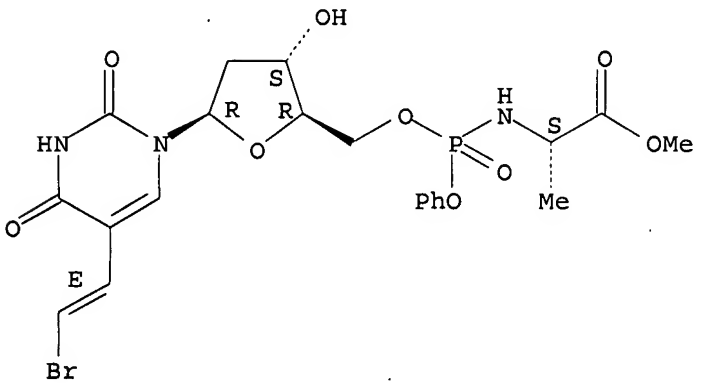
or IAP-2 genes and a chemotherapeutic agent, and compns. and kits·thereof, for the treatment of proliferative diseases. The invention further claims sequences for nucleobase oligomers that are antisense IAP (inhibitor of apoptosis protein) oligomers. The antisense IAP nucleobase oligomers specifically hybridize with polynucleotides encoding an IAP and reduce the amount of an IAP protein produced in a cell. Thus by reducing the IAP protein, the invention provides methods for inducing cancer cells to undergo apoptosis and for overriding anti-apoptotic signals in cancer cells. As an example of the invention, mice with s.c. H460 human lung carcinoma xenografts were injected intratumorally with XIAP antisense mixed-base 2'-O-Me RNA oligonucleotides (C5 and/or G4) and the drug vinorelbine. At the end of the 24 d treatment period, the mean relative tumor growth was reduced .apprx.70% in treated mice. The inhibition of tumor growth was correlated with down-regulation of human XIAP protein expression and an increased number of dead cells. The mice did not show any signs of cytotoxicity such as body weight loss.

IT 232925-18-7, Thymectacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sequences of antisense IAP (inhibitor of apoptosis protein) oligomers and their use for treatment of proliferative diseases with chemotherapeutic agent)

RN 232925-18-7 CAPLUS

CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:36552 CAPLUS
DOCUMENT NUMBER: 142:107396
TITLE: Use of antivirals against inflammatory bowel diseases
INVENTOR(S): Brantl, Victor
PATENT ASSIGNEE(S): ICN Pharmaceuticals Switzerland Ltd., Switz.
SOURCE: U.S. Pat. Appl. Publ., 14 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005009848	A1	20050113	US 2003-618176	20030710
WO 2005004873	A1	20050120	WO 2004-CH431	20040708

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-618176 A 20030710

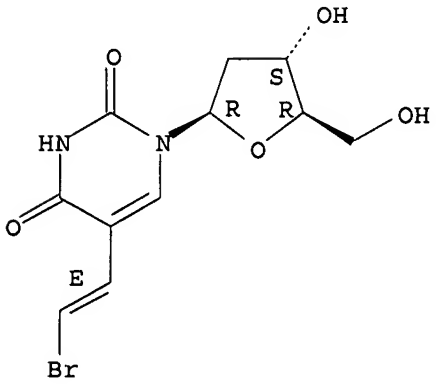
AB A method for the prophylaxis or treatment of an inflammatory bowel disease is provided, comprising administering to a patient having or at risk of developing an inflammatory bowel disease a therapeutically or preventatively effective amount of one or more antivirals selected from the group consisting of an antiviral active against herpes viruses, pharmaceutically acceptable salts thereof, and mixts. thereof, excluding anti-inflammatory agents selected from the group consisting of salicylates and salicylates prodrugs. The antiviral may be used in combination with addnl. active agents effective against inflammatory bowel disease.

IT 69304-47-8, Brivudine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of antivirals against IBD)

RN 69304-47-8 CAPLUS

CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L9 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN

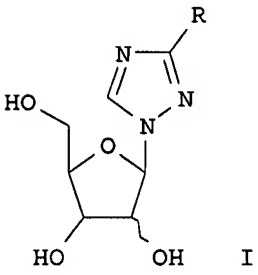
ACCESSION NUMBER: 2005:36543 CAPLUS
DOCUMENT NUMBER: 142:107410
TITLE: Use of ribofuranose derivatives against inflammatory bowel diseases
INVENTOR(S): Brantl, Victor
PATENT ASSIGNEE(S): ICN Pharmaceuticals Switzerland Ltd., Switz.; Valeant Research & Development
SOURCE: U.S. Pat. Appl. Publ., 14 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 2005009766	A1	20050113	US 2003-618148	20030710
US 6930093	B2	20050816		
WO 2005004881	A1	20050120	WO 2004-CH430	20040708
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005009767	A1	20050113	US 2004-902423	20040729
US 2005009768	A1	20050113	US 2004-902757	20040729
US 2005153907	A1	20050714	US 2004-995595	20041122
US 2005153908	A1	20050714	US 2004-995607	20041122

PRIORITY APPLN. INFO.: US 2003-618148 A 20030710

GI



I

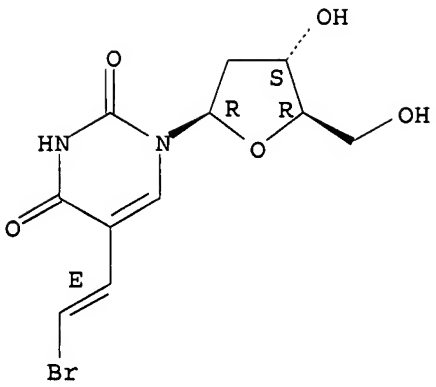
AB A method for the prophylaxis or treatment of an inflammatory bowel disease is provided, comprising administering to a patient having or at risk of developing an inflammatory bowel disease a therapeutically or preventatively effective amount of one or more ribofuranose derivs. I (R = carboxamide, amidine) and pharmaceutically acceptable acid addition salts thereof, and the configuration at the C2 carbon of the ribofuranose moiety is D or L. I may be used in combination with further active agents such as antivirals or agents effective against inflammatory bowel disease. Ribavirin was effective in a rat model for inflammatory bowel disease.

IT 69304-47-8, Brivudine
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as antiviral agent in combination; ribofuranose derivs. for treatment of inflammatory bowel diseases)

RN 69304-47-8 CAPLUS

CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



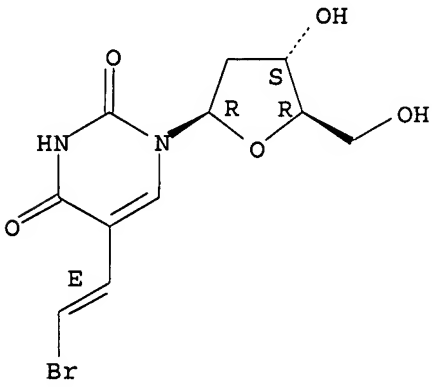
L9 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN.
ACCESSION NUMBER: 2004:822752 CAPLUS
DOCUMENT NUMBER: 141:307514
TITLE: Gene expression-based method for reinforcement of the apoptotic effect of anticancer drugs without an increase of toxic side effects
INVENTOR(S): Fahrig, Rudolf; Heinrich, Jorg-Christian; Krupitza, Georg
PATENT ASSIGNEE(S): Resprotect G.m.b.H., Germany
SOURCE: Ger. Offen., 9 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10313035	A1	20041007	DE 2003-10313035	20030324
CA 2519801	A1	20041007	CA 2003-2519801	20031120
WO 2004084917	A1	20041007	WO 2003-EP13008	20031120
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003296589	A1	20041018	AU 2003-296589	20031120
EP 1605952	A1	20051221	EP 2003-816433	20031120
EP 1605952	B1	20070502		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003018204	A	20060321	BR 2003-18204	20031120
CN 1758918	A	20060412	CN 2003-80110201	20031120
JP 2006521283	T	20060921	JP 2004-569859	20031120
AT 361081	T	20070515	AT 2003-816433	20031120
US 2006178338	A1	20060810	US 2006-550013	20060404
PRIORITY APPLN. INFO.:			DE 2003-10313035 A	20030324
			WO 2003-EP13008 W	20031120

AB The invention discloses the use of at least one inhibitor of overexpression of DNA repair genes and oncogenes for the production of a drug for reinforcement of the apoptotic effect of anticancer drugs after chemotherapy.

IT 69304-47-8, BVDU
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gene expression-based method for reinforcement of apoptotic effect of anticancer drugs without increase of toxic side effects)
RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L11 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:822752 CAPLUS
DOCUMENT NUMBER: 141:307514
TITLE: Gene expression-based method for reinforcement of the apoptotic effect of anticancer drugs without an increase of toxic side effects
INVENTOR(S): Fahrig, Rudolf; Heinrich, Jorg-Christian; Krupitza, Georg
PATENT ASSIGNEE(S): Resprotect G.m.b.H., Germany
SOURCE: Ger. Offen., 9 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

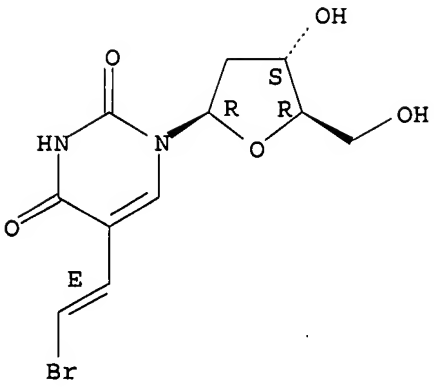
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10313035	A1	20041007	DE 2003-10313035	20030324
CA 2519801	A1	20041007	CA 2003-2519801	20031120
WO 2004084917	A1	20041007	WO 2003-EP13008	20031120
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003296589	A1	20041018	AU 2003-296589	20031120
EP 1605952	A1	20051221	EP 2003-816433	20031120
EP 1605952	B1	20070502		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003018204	A	20060321	BR 2003-18204	20031120
CN 1758918	A	20060412	CN 2003-80110201	20031120
JP 2006521283	T	20060921	JP 2004-569859	20031120
AT 361081	T	20070515	AT 2003-816433	20031120
US 2006178338	A1	20060810	US 2006-550013	20060404
PRIORITY APPLN. INFO.:			DE 2003-10313035 A	20030324
			WO 2003-EP13008 W	20031120

AB The invention discloses the use of at least one inhibitor of overexpression of DNA repair genes and oncogenes for the production of a drug for reinforcement of the apoptotic effect of anticancer drugs after chemotherapy.

IT 69304-47-8, BVDU
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gene expression-based method for reinforcement of apoptotic effect of anticancer drugs without increase of toxic side effects)

RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.


OH
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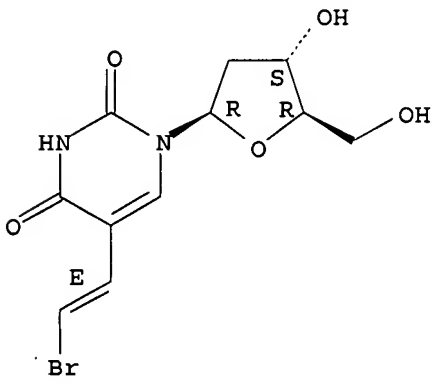
L15 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:780065 CAPLUS
DOCUMENT NUMBER: 140:104666
TITLE: Inhibition of Induced Chemoresistance by Cotreatment with (E)-5-(2-Bromovinyl)-2'-Deoxyuridine (RP101)
AUTHOR(S): Fahrig, Rudolf; Heinrich, Joerg-Christian; Nickel, Bernd; Wilfert, Falk; Leisser, Christina; Krupitza, Georg; Praha, Christian; Sonntag, Denise; Fiedler, Beate; Scherthan, Harry; Ernst, Heinrich
CORPORATE SOURCE: RESprotect, Dresden, D-01307, Germany
SOURCE: Cancer Research (2003), 63(18), 5745-5753
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB VInduced chemoresistance leads to the reduction of apoptotic responses. Although several drugs are in development that circumvent or decrease existing chemoresistance, none has the potential to prevent or reduce its induction. Here, we present data from a drug that could perhaps fill this gap. Cotreatment of chemotherapy with (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU, RP101) prevented the decrease of apoptotic effects during the course of chemotherapy and reduced nonspecific toxicity. Amplification of chemoresistance genes (Mdr1 and Dhfr) and overexpression of gene products involved in proliferation (DDX1) or DNA repair (UBE2N and APEX) were inhibited, whereas activity of NAD(P)H: quinone oxidoreductase 1 (NQO1) was enhanced. During recovery, when treatment was with BVDU only, microfilamental proteins were up-regulated, and proteins involved in ATP generation or cell survival (STAT3 and JUN-D) were down-regulated. That way, in three different rat tumor models, the antitumor efficiency of chemotherapy was optimized, and toxic side effects were reduced. Because of these beneficial properties of BVDU, a clin. pilot Phase I/II study with five human tumor entities has been started at the University of Dresden (Dresden, Germany). So far, no unwanted side effects have been observed
IT 69304-47-8, BVDU
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of chemoresistance by cotreatment with (E)-5-(2-bromovinyl)-2'-deoxyuridine)
RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

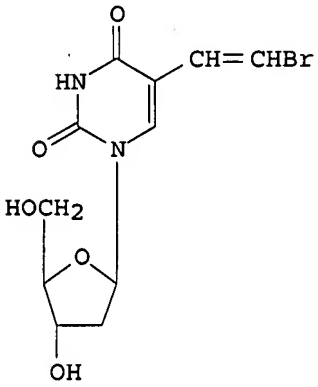
Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:566681 CAPLUS
DOCUMENT NUMBER: 111:166681
TITLE: Bioanalysis of (E)-5-(2-bromovinyl)-2'-deoxyuridine in plasma
AUTHOR(S): Reeuwijk, H. J. E. M.; Tjaden, U. R.; De Bruijn, E. A.; Van der Greef, J.
CORPORATE SOURCE: Cent. Bio-Pharm. Sci., Univ. Leiden, Leiden, Neth.
SOURCE: Chromatogram (1989), 10(2), 2-3
CODEN: CHROEY; ISSN: 1053-8097
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



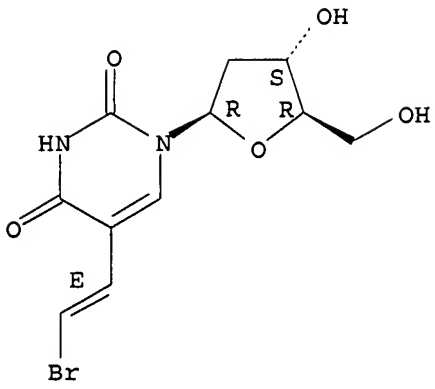
I

AB A reversed phase HPLC system with a simplified sample pretreatment is described for the routine anal. of (E)-5-(2-bromovinyl)-2'-deoxyuridine (I) in blood plasma levels of human patients undergoing chemotherapy. Because of the high protein binding of I, deproteination by adding HClO4 is required. After centrifugation, the supernatant is injected directly onto the HPLC system. Chromatog. was carried out on an ultrasphere XL Octyl column with a mobile phase consisting of 25% MeOH in a 10 mM HClO4 system. A photodiode array detection system was used. I could be separated from its metabolite bromovinyluridine as well as from 5-fluorouracil and its metabolites. Max detection was obtained at 307 nm. The method is fast with 75% recovery and a detection limit of 8 ng (20 ng/mL in plasma), which is sufficiently low for pharmacokinetic studies.

IT 69304-47-8, (E)-5-(2-Bromovinyl)-2'-deoxyuridine
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in blood of humans by HPLC)

RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L15 ANSWER 3 OF 3 MEDLINE on STN
ACCESSION NUMBER: 2003460324 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14522895
TITLE: Inhibition of induced chemoresistance by cotreatment with (E)-5-(2-bromovinyl)-2'-deoxyuridine (RP101).
AUTHOR: Fahrig Rudolf; Heinrich Jorg-Christian; Nickel Bernd; Wilfert Falk; Leisser Christina; Krupitza Georg; Praha Christian; Sonntag Denise; Fiedler Beate; Scherthan Harry; Ernst Heinrich
CORPORATE SOURCE: RESprotect, Dresden, Germany.. fahrig@resprotect.de
SOURCE: Cancer research, (2003 Sep 15) Vol. 63, No. 18, pp. 5745-53.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 3 Oct 2003
Last Updated on STN: 18 Dec 2003
Entered Medline: 4 Dec 2003

AB Induced chemoresistance leads to the reduction of apoptotic responses. Although several drugs are in development that circumvent or decrease existing chemoresistance, none has the potential to prevent or reduce its induction. Here, we present data from a drug that could perhaps fill this gap. Cotreatment of chemotherapy with (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU, RP101) prevented the decrease of apoptotic effects during the course of chemotherapy and reduced nonspecific toxicity. Amplification of chemoresistance genes (Mdr1 and Dhfr) and overexpression of gene products involved in proliferation (DDX1) or DNA repair (UBE2N and APEX) were inhibited, whereas activity of NAD(P)H: quinone oxidoreductase 1 (NQO1) was enhanced. During recovery, when treatment was with BVDU only, microfilamental proteins were up-regulated, and proteins involved in ATP generation or cell survival (STAT3 and JUN-D) were down-regulated. That way, in three different rat tumor models, the antitumor efficiency of chemotherapy was optimized, and toxic side effects were reduced. Because of these beneficial properties of BVDU, a clinical pilot Phase I/II study with five human tumor entities has been started at the University of Dresden (Dresden, Germany). So far, no unwanted side effects have been observed.

L17 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:695764 CAPLUS
DOCUMENT NUMBER: 137:210932
TITLE: Combination therapy for reduction of toxicity of chemotherapeutic agents
INVENTOR(S): Prendergast, Patrick T.
PATENT ASSIGNEE(S): Ire.
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

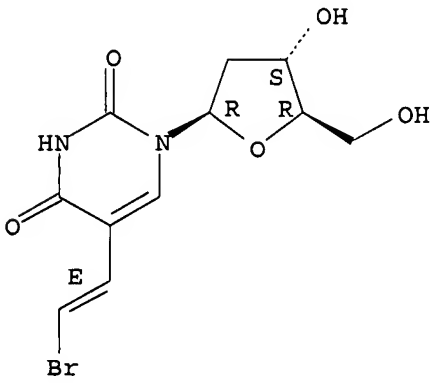
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002069949	A2	20020912	WO 2002-IB632	20020305
WO 2002069949	A3	20030605		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002238799	A1	20020919	AU 2002-238799	20020305
US 2002169140	A1	20021114	US 2002-91855	20020306
PRIORITY APPLN. INFO.:			IE 2001-209 A	20010306
			WO 2002-IB632 W	20020305

AB Provided in the present invention are compds. suitable for treating neoplasms and tumors, viral, bacterial and parasite infections and combination therapy with these agents to lower the adverse side effects.

IT 69304-47-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy for reduction of toxicity of chemotherapeutic agents)

RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



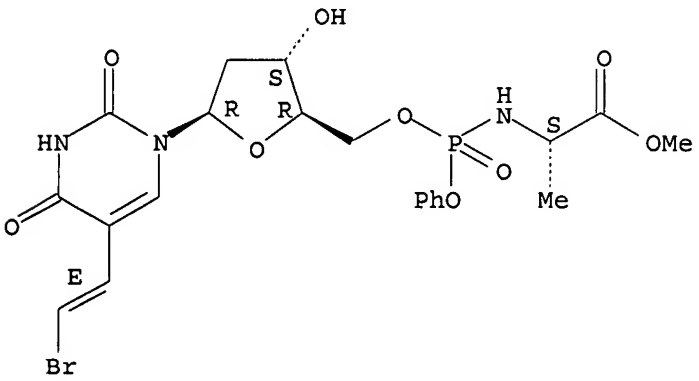
L17 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:694508 CAPLUS
DOCUMENT NUMBER: 138:248065
TITLE: Nucleoside transport inhibitors, dipyridamole and p-nitrobenzylthioinosine, selectively potentiate the antitumor activity of NB1011
AUTHOR(S): Boyer, Christopher R.; Karjian, Patricia L.; Wahl, Geoffrey M.; Pegram, Mark; Neuteboom, Saskia T. C.
CORPORATE SOURCE: NewBiotics, Inc, San Diego, CA, 92121, USA
SOURCE: Anti-Cancer Drugs (2002), 13(1), 29-36
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB NB1011, a novel anticancer agent, targets tumor cells expressing high levels of thymidylate synthase (TS). NB1011 is converted intracellularly to bromovinyldeoxyuridine monophosphate (BVdUMP) which competes with the natural substrate, deoxyuridine monophosphate, for binding to TS. Unlike inhibitors, NB1011 becomes a reversible substrate for TS catalysis. Thus, TS retains activity and converts BVdUMP into cytotoxic product(s). In vitro cytotoxicity studies demonstrate NB1011's preferential activity against tumor cells expressing elevated TS protein levels. Addnl., NB1011 has antitumor activity in vivo. To identify drugs which interact synergistically with NB1011, we screened 13 combinations of chemotherapeutic agents with NB1011 in human tumor and normal cells. Dipyridamole and p-nitrobenzylthioinosine (NBMPR), potent inhibitors of equilibrative nucleoside transport, synergized with NB1011 selectively against 5-fluorouracil (5-FU)-resistant H630R10 colon carcinoma cells [combination index (CI)=0.75 and 0.35] and Tomudex-resistant MCF7TDX breast carcinoma cells (CI=0.51 and 0.57), both TS overexpressing cell lines. These agents produced no synergy with NB1011 in Det551 and CCD18co normal cells (CI > 1.1) lacking TS overexpression. Dipyridamole potentiated NB1011's cytotoxicity in medium lacking nucleosides and bases, suggesting a non-salvage-dependent mechanism. We demonstrate that nucleoside transport inhibitors, dipyridamole and NBMPR, show promise for clin. efficacious combination with NB1011.

IT 232925-18-7, NB1011
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipyridamole and nitrobenzylthioinosine potentiate antitumor activity of NB1011)

RN 232925-18-7 CAPLUS
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

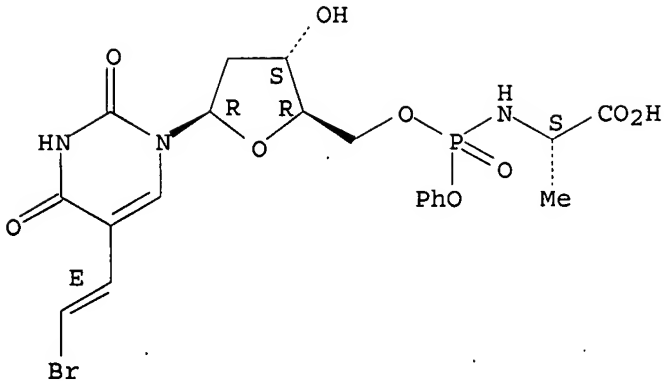
L17 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:391469 CAPLUS
DOCUMENT NUMBER: 136:386347
TITLE: Preparation of synergistic enzyme catalyzed therapeutic activation (ECTA) nucleosides as antitumor agents
INVENTOR(S): Shepard, H. Michael; Boyer, Christopher
PATENT ASSIGNEE(S): Newbiotics, Inc., USA
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002039952	A2	20020523	WO 2001-US43566	20011116
WO 2002039952	A3	20021010		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002036455	A5	20020527	AU 2002-36455	20011116
US 2002147175	A1	20021010	US 2001-990799	20011116
PRIORITY APPLN. INFO.:			US 2000-249722P P	20001116
			WO 2001-US43566 W	20011116

AB This invention provides compns. containing an effective amount of a novel substrate compound that selectively inhibit the proliferation of hyper-proliferative cells, for example, pathol. cells that endogenously over-express a target enzyme that confers resistance to biol. and chemo-therapeutic agents and an effective amount of a nucleoside transport antagonistic agents. Further provided by this invention is a method for treating a subject by delivering to the subject the composition as described herein. The compns. of this invention may be used alone or in combination with other chemo-therapeutics or alternative anti-cancer therapies such as radiation. Thus, (E)-5-(2-bromovinyl)-2'-deoxy-5'-uridyl Ph L-alaninylphosphoramidate (I) was prepared and tested in vitro human cells as synergistic antitumor agent. Vinblastine and doxorubicin showed potential synergy (CI < 1.1) with I in MCF7TDX and H630R10 cell. Irinotecan and taxol showed an additive or antagonistic interaction (CI = 1-1.4). The most antagonistic interaction was observed with 5-fluorouracil which gave CI = 3.19 in MCF7TDX cells. In light of these results, vinblastine and doxorubicin were chosen for further study.

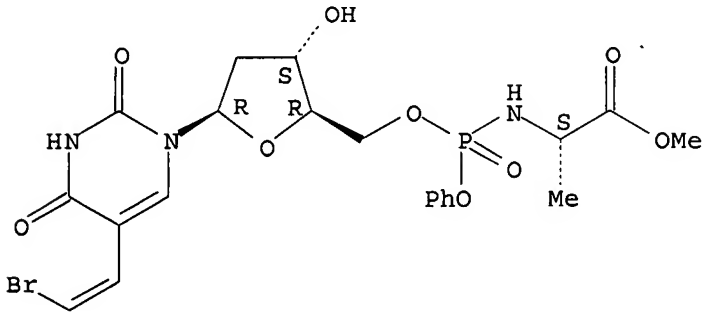
IT 321982-16-5P 322454-65-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)
RN 321982-16-5 CAPLUS
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



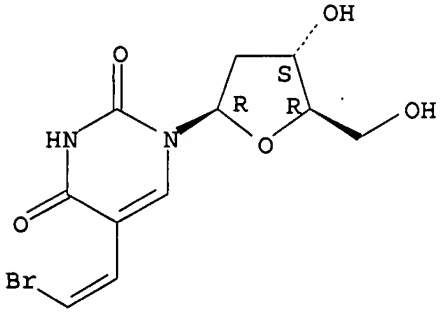
RN 322454-65-9 CAPLUS
CN L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



IT 82768-44-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)
RN 82768-44-3 CAPLUS
CN Uridine, 5-(2-bromoethenyl)-2'-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L17 ANSWER 4 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2003460324 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14522895

TITLE: Inhibition of induced chemoresistance by cotreatment with (E)-5-(2-bromovinyl)-2'-deoxyuridine (RP101).
AUTHOR: Fahrig Rudolf; Heinrich Jorg-Christian; Nickel Bernd; Wilfert Falk; Leisser Christina; Krupitza Georg; Praha Christian; Sonntag Denise; Fiedler Beate; Scherthan Harry; Ernst Heinrich
CORPORATE SOURCE: RESprotect, Dresden, Germany.. fahrig@resprotect.de
SOURCE: Cancer research, (2003 Sep 15) Vol. 63, No. 18, pp. 5745-53.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 3 Oct 2003
Last Updated on STN: 18 Dec 2003
Entered Medline: 4 Dec 2003

AB Induced chemoresistance leads to the reduction of apoptotic responses. Although several drugs are in development that circumvent or decrease existing chemoresistance, none has the potential to prevent or reduce its induction. Here, we present data from a drug that could perhaps fill this gap. Cotreatment of chemotherapy with (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU, RP101) prevented the decrease of apoptotic effects during the course of chemotherapy and reduced nonspecific toxicity. Amplification of chemoresistance genes (Mdr1 and Dhfr) and overexpression of gene products involved in proliferation (DDX1) or DNA repair (UBE2N and APEX) were inhibited, whereas activity of NAD(P)H: quinone oxidoreductase 1 (NQO1) was enhanced. During recovery, when treatment was with BVDU only, microfilamental proteins were up-regulated, and proteins involved in ATP generation or cell survival (STAT3 and JUN-D) were down-regulated. That way, in three different rat tumor models, the antitumor efficiency of chemotherapy was optimized, and toxic side effects were reduced. Because of these beneficial properties of BVDU, a clinical pilot Phase I/II study with five human tumor entities has been started at the University of Dresden (Dresden, Germany). So far, no unwanted side effects have been observed.

L17 ANSWER 5 OF 8 MEDLINE on STN
ACCESSION NUMBER: 88192709 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3358790
TITLE: Enhancing effect of bromovinyldeoxyuridine on antitumor activity of 5-fluorouracil against adenocarcinoma 755 in mice. Increased therapeutic index and correlation with increased plasma 5-fluorouracil levels.
AUTHOR: Iigo M; Araki E; Nakajima Y; Hoshi A; De Clercq E
CORPORATE SOURCE: Chemotherapy Division, National Cancer Center Research Institute, Tokyo, Japan.
SOURCE: Biochemical pharmacology, (1988 Apr 15) Vol. 37, No. 8, pp. 1609-13.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198805
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 29 Jan 1996
Entered Medline: 17 May 1988

AB A marked inhibition of the growth of solid tumor adenocarcinoma 755 was

achieved by the combination of 5-fluorouracil (5-FU) with bromovinyldeoxyuridine (BVDU). The therapeutic index (LD50/ED50) for the combination of BVDU plus 5-FU was 8.1 and 3.9 upon intraperitoneal (i.p.) or oral (p.o.) administration, respectively. The therapeutic index of i.p. 5-FU given alone was 2.3, whereas for p.o. 5-FU given alone no therapeutic index could be established because of insufficient activity of the compound. Thus, the therapeutic index of 5-FU increased significantly when combined with BVDU. Pharmacokinetic studies revealed that upon i.p. or p.o. 5-FU administration plasma 5-FU levels rapidly declined, but that, in the combination with BVDU, the plasma clearance of 5-FU, especially following p.o. administration, was slowed down considerably. Antitumor activity of 5-FU correlated with AUC (area under the concentration x time curve), within the plasma 5-FU concentration range from 0.02 to 0.4 microgram/ml.

L17 ANSWER 6 OF 8 MEDLINE on STN
ACCESSION NUMBER: 88004642 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3115784
TITLE: Enhancing effect of bromovinyldeoxyuridine on antitumor activity of 5-fluorouracil and ftorafur against adenocarcinoma 755 in mice.
AUTHOR: Iigo M; Nakajima Y; Hoshi A; De Clercq E
CORPORATE SOURCE: Pharmacology Division, National Cancer Center Research Institute, Tokyo, Japan.
SOURCE: European journal of cancer & clinical oncology, (1987 Jun) Vol. 23, No. 6, pp. 773-7.
Journal code: 8112045. ISSN: 0277-5379.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198710
ENTRY DATE: Entered STN: 5 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 29 Oct 1987

AB When combined with bromovinyldeoxyuridine (BVdUrd), 5-fluorouracil (FUra) brought about a significant reduction in the growth of adenocarcinoma 755 tumors in mice, at doses at which either drug used alone (BVdUrd: 100 mg/kg) did not effect an appreciable antitumor activity. BVdUrd also increased the toxicity of FUra for the hosts but not commensurately with its enhancing effect on the antitumor activity of FUra. BVdUrd also potentiated the antitumor activity of ftorafur, so that doses of ftorafur (50 or 100 mg/kg) which by themselves did not cause a significant reduction in tumor growth became markedly effective when combined with BVdUrd at a dose as low as 10 mg/kg. For some combinations of BVdUrd with FUra, the antitumor potency was further enhanced by the administration of L-cysteine (300 mg/kg).

L17 ANSWER 7 OF 8 MEDLINE on STN
ACCESSION NUMBER: 87221897 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3108221
TITLE: The antitumor potency of oral tegafur against adenocarcinoma 755 in mice is markedly enhanced by oral (E)-5-(2-bromovinyl)-2'-deoxyuridine.
AUTHOR: Iigo M; Yamaizumi Z; Nishimura S; Hoshi A; De Clercq E
SOURCE: Japanese journal of cancer research : Gann, (1987 Apr) Vol. 78, No. 4, pp. 409-13.
Journal code: 8509412. ISSN: 0910-5050.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 198707
ENTRY DATE: Entered STN: 5 Mar 1990
Last Updated on STN: 5 Mar 1990
Entered Medline: 16 Jul 1987

AB A significant inhibition of the growth of adenocarcinoma 755 tumors in BDF1 mice was effected by oral tegafur (FT) in combination with oral (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVdUrd), at doses at which neither drug used alone had antitumor activity. The maximum inhibition of tumor growth (97%) was achieved by using a combination of 50 mg FT/kg with 10 mg BVdUrd/kg but, even at a dose as low as 1 mg BVdUrd/kg, the antitumor potency of FT was enhanced. The effect which BVdUrd has on the antitumor potency of FT is apparently due to inhibitory action by bromovinyluracil, the phosphorolytic product of BVdUrd, on the degradation of 5-fluorouracil, the oxidative product of FT, by dihydrothymine dehydrogenase.

L17 ANSWER 8 OF 8 MEDLINE on STN
ACCESSION NUMBER: 86321791 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3752935
TITLE: Potential of bromovinyldeoxyuridine in anticancer chemotherapy.
AUTHOR: De Clercq E
SOURCE: Anticancer research, (1986 Jul-Aug) Vol. 6, No. 4, pp. 549-56.
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198610
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 10 Oct 1986

AB Bromovinyldeoxyuridine (BVDU) is a highly potent and selective antiherpetic agent which offers great potential for the treatment of severe herpes simplex virus type 1 (HSV-1) and varicella-zoster virus (VZV) infections in cancer patients. BVDU inhibits the replication of HSV-1 and VZV at a concentration as low as 1-10 ng/ml; and the proliferation of tumor cells transformed with the HSV-1 thymidine kinase gene is even inhibited by BVDU concentrations lower than 1 ng/ml. Moreover, BVDU is inhibitory to Epstein-Barr virus replication in vitro at a concentration of 0.02 micrograms/ml. Due to the action of pyrimidine nucleoside phosphorylases, BVDU is rapidly degraded to the free pyrimidine base bromovinyluracil (BVU). In contrast to BVDU, which is cleared from the bloodstream within 2-3 hours, BVU persists in the plasma for at least 24 hours. During this period BVU can be converted again to BVDU upon administration of deoxythymidine, deoxyuridine or any other deoxyribonucleoside capable of transferring its deoxyribosyl moiety onto BVU. BVU owes its long persistence in the bloodstream to the fact that it does not act as substrate for dihydrothymine dehydrogenase, the enzyme that catalyzes the first step in the catabolic pathway of pyrimidines. On the contrary, BVU acts as an efficient inhibitor of this enzyme and thereby prevents the degradation of fluorouracil (FU), a well-known anticancer agent. As a consequence, BVDU via BVU enhances the antitumor activity of FU, as has been demonstrated in the murine P388 leukemia model. Thus, BVDU may be useful in anticancer chemotherapy from several viewpoints, e.g. for treatment of intercurrent herpesvirus infections, and, in combination with FU, for treatment of those malignant diseases that are amenable to FU therapy.

L19 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:822752 CAPLUS
DOCUMENT NUMBER: 141:307514
TITLE: Gene expression-based method for reinforcement of the apoptotic effect of anticancer drugs without an increase of toxic side effects
INVENTOR(S): Fahrig, Rudolf; Heinrich, Jorg-Christian; Krupitza, Georg
PATENT ASSIGNEE(S): Resprotect G.m.b.H., Germany
SOURCE: Ger. Offen., 9 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10313035	A1	20041007	DE 2003-10313035	20030324
CA 2519801	A1	20041007	CA 2003-2519801	20031120
WO 2004084917	A1	20041007	WO 2003-EP13008	20031120
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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AU 2003296589	A1	20041018	AU 2003-296589	20031120
EP 1605952	A1	20051221	EP 2003-816433	20031120
EP 1605952	B1	20070502		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003018204	A	20060321	BR 2003-18204	20031120
CN 1758918	A	20060412	CN 2003-80110201	20031120
JP 2006521283	T	20060921	JP 2004-569859	20031120
AT 361081	T	20070515	AT 2003-816433	20031120
US 2006178338	A1	20060810	US 2006-550013	20060404

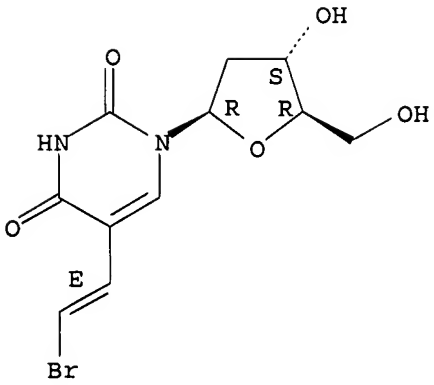
PRIORITY APPLN. INFO.: DE 2003-10313035 A 20030324
WO 2003-EP13008 W 20031120

AB The invention discloses the use of at least one inhibitor of overexpression of DNA repair genes and oncogenes for the production of a drug for reinforcement of the apoptotic effect of anticancer drugs after chemotherapy.

IT 69304-47-8, BVDU
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gene expression-based method for reinforcement of apoptotic effect of anticancer drugs without increase of toxic side effects)

RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

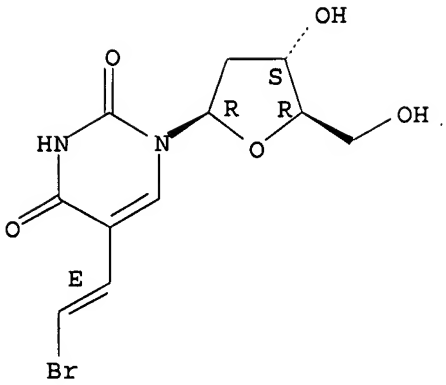


L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:780065 CAPLUS
DOCUMENT NUMBER: 140:104666
TITLE: Inhibition of Induced Chemoresistance by Cotreatment with (E)-5-(2-Bromovinyl)-2'-Deoxyuridine (RP101)
AUTHOR(S): Fahrig, Rudolf; Heinrich, Joerg-Christian; Nickel, Bernd; Wilfert, Falk; Leisser, Christina; Krupitza, Georg; Praha, Christian; Sonntag, Denise; Fiedler, Beate; Scherthan, Harry; Ernst, Heinrich
CORPORATE SOURCE: RESprotect, Dresden, D-01307, Germany
SOURCE: Cancer Research (2003), 63(18), 5745-5753
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB VInduced chemoresistance leads to the reduction of apoptotic responses. Although several drugs are in development that circumvent or decrease existing chemoresistance, none has the potential to prevent or reduce its induction. Here, we present data from a drug that could perhaps fill this gap. Cotreatment of chemotherapy with (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU, RP101) prevented the decrease of apoptotic effects during the course of chemotherapy and reduced nonspecific toxicity. Amplification of chemoresistance genes (Mdr1 and Dhfr) and overexpression of gene products involved in proliferation (DDX1) or DNA repair (UBE2N and APEX) were inhibited, whereas activity of NAD(P)H: quinone oxidoreductase 1 (NQO1) was enhanced. During recovery, when treatment was with BVDU only, microfilamental proteins were up-regulated, and proteins involved in ATP generation or cell survival (STAT3 and JUN-D) were down-regulated. That way, in three different rat tumor models, the antitumor efficiency of chemotherapy was optimized, and toxic side effects were reduced. Because of these beneficial properties of BVDU, a clin. pilot Phase I/II study with five human tumor entities has been started at the University of Dresden (Dresden, Germany). So far, no unwanted side effects have been observed

IT 69304-47-8, BVDU
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of chemoresistance by cotreatment with (E)-5-(2-bromovinyl)-2'-deoxyuridine)
RN 69304-47-8 CAPLUS
CN Uridine, 5-[(1E)-2-bromoethenyl]-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 3 MEDLINE on STN
ACCESSION NUMBER: 84208188 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6539202
TITLE: Oral (E)-5-(2-bromovinyl)-2'-deoxyuridine treatment of severe herpes zoster in cancer patients.
AUTHOR: Wildiers J; De Clercq E
SOURCE: European journal of cancer & clinical oncology, (1984 Apr) Vol. 20, No. 4, pp. 471-6.
Journal code: 8112045. ISSN: 0277-5379.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198407
ENTRY DATE: Entered STN: 20 Mar 1990
Last Updated on STN: 20 Mar 1990
Entered Medline: 13 Jul 1984

AB BVDU [(E)-5-(2-bromovinyl)-2'-deoxyuridine] is a highly potent and selective anti-herpes drug. It is particularly active against Varicella zoster virus, as demonstrated in cell culture and animals (monkeys). BVDU has been administered orally, at a dose of 7.5 mg/kg/day for 5 days, to 20 patients with severe localised or disseminated Herpes zoster. All patients had a malignant disorder for which they had been given intensive chemo- or radiotherapy. Upon BVDU treatment a rapid cessation of the acute Herpes zoster episode was noted in all but one patient. In the majority of patients progression of the infection was arrested within 1 day of starting treatment. No toxic side-effects could be attributed to the drug at the dosage used.

L24 ANSWER 12 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2006664897 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17001178
TITLE: RP101 improves the efficacy of chemotherapy in pancreas carcinoma cell lines and pancreatic cancer patients.
AUTHOR: Fahrig Rudolf; Quietzsch Detlef; Heinrich Jorg-Christian; Heinemann Volker; Boeck Stefan; Schmid Roland M; Praha Christian; Liebert Andreas; Sonntag Denise; Krupitza Georg; Hanel Mathias
CORPORATE SOURCE: RESprotect, Dresden Germany.. fahrig@resprotect.de
SOURCE: Anti-cancer drugs, (2006 Oct) Vol. 17, No. 9, pp. 1045-56. Journal code: 9100823. ISSN: 0959-4973.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200612
ENTRY DATE: Entered STN: 15 Nov 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 4 Dec 2006

AB RP101 [(E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)], which supports apoptosis and prevents the acquisition of chemoresistance, was tested in cultured human pancreatic tumor cells. RP101 downregulated uridine phosphorylase, a marker of poor prognosis, and APEX1, which is involved in DNA repair, and repressed Stat3 and its target vascular endothelial growth factor. Furthermore, RP101 activated antitumor immunity as demonstrated by enhanced cytolytic activity of NK-92 natural killer cells. This was concomitant with an enhanced expression of lymphotoxins alpha and beta, natural killer cell transcript 4, tumor necrosis factor LIGHT/TNFSF-14, and intercellular adhesion molecule-1 in pancreas carcinoma cells. These results encouraged us to investigate the effect of RP101 in pancreas cancer patients. Here, we present data from two RP101 combination therapy schemes. In a first pilot study, 13 patients in stage III and VI of the disease were treated with gemcitabine +cisplatin+RP101. RP101 co-treatment enhanced remissions, survival and time to progression. Seventy-seven percent of the patients lived or have lived longer than 1 year, and 23% have lived more than 2 years. Median survival was 447 days, time to progression 280 days and the response rate 33%. A second study with 21 patients in similar stages of disease, treated with RP101+gemcitabine alone, confirmed the results of the pilot study. Eighty-three percent of the presently evaluable patients live or lived 0.5 years or longer and 33% 1 year or longer. Considering both studies, the tumor control was 94%. The data indicate that acquisition of chemoresistance was prevented and the antitumor efficacy of standard chemotherapy was improved. To our knowledge, RP101 co-treatment is more efficient than any other regimen published.

L24 ANSWER 13 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2004551428 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15389733
TITLE: (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU).
AUTHOR: De Clercq Erik
CORPORATE SOURCE: Department of Microbiology and Immunology, Division of Virology and Chemotherapy, Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium.. erik.declercq@rega.kuleuven.ac.be
SOURCE: Medicinal research reviews, (2005 Jan) Vol. 25, No. 1, pp. 1-20. Ref: 116
Journal code: 8103150. ISSN: 0198-6325.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 4 Nov 2004
Last Updated on STN: 1 Apr 2005
Entered Medline: 31 Mar 2005

AB (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU, Brivudin, Zostex, Zerpex, Zonavir), now more than 20 years after its discovery, still stands out as a highly potent and selective inhibitor of herpes simplex virus type 1 (HSV-1) and varicella-zoster virus (VZV) infections. It has been used in the topical treatment of herpetic keratitis and recurrent herpes labialis and the systemic (oral) treatment of herpes zoster (zona, shingles). The high selectivity of BVDU towards HSV-1 and VZV depends primarily on a specific phosphorylation of BVDU to its 5'-diphosphate (DP) by the virus-encoded thymidine kinase (TK). After further phosphorylation (by cellular enzymes), to the 5'-triphosphate (TP), the compound interferes as a competitive inhibitor/alternate substrate with the viral DNA polymerase. The specific phosphorylation by the HSV- and VZV-induced TK also explains the marked cytostatic activity of BVDU against tumor cells that have been transduced by the viral TK genes. This finding offers considerable potential in a combined gene therapy/chemotherapy approach for cancer. To the extent that BVDU or its analogues (i.e., BVaraU) are degraded (by thymidine phosphorylase) to (E)-5-(2-bromovinyl)uracil (BVU), they may potentiate the anticancer potency, as well as toxicity, of 5-fluorouracil. This ensues from the direct inactivating effect of BVU on dihydropyrimidine dehydrogenase, the enzyme that initiates the degradative pathway of 5-fluorouracil. The prime determinant in the unique behavior of BVDU is its (E)-5-(2-bromovinyl) substituent. Numerous BVDU analogues have been described that, when equipped with this particular pharmacophore, demonstrate an activity spectrum characteristic of BVDU, including selective anti-VZV activity.

L24 ANSWER 14 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2001663539 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11708804
TITLE: Nucleoside analog cytotoxicity and bystander cell killing of cancer cells expressing Drosophila melanogaster deoxyribonucleoside kinase in the nucleus or cytosol.
AUTHOR: Zheng X; Johansson M; Karlsson A
CORPORATE SOURCE: Karolinska Institute, Division of Clinical Virology, Huddinge University Hospital, S-141 86 Stockholm, Sweden.
SOURCE: Biochemical and biophysical research communications, (2001 Nov 23) Vol. 289, No. 1, pp. 229-33.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 19 Nov 2001
Last Updated on STN: 23 Jan 2002
Entered Medline: 27 Dec 2001

AB We have recently shown that the overexpression of Drosophila melanogaster multisubstrate deoxyribonucleoside kinase (Dm-dNK) in cancer cell lines increases the cells' sensitivity to several cytotoxic nucleoside analogs and the enzyme may accordingly be used as a suicide gene in combined gene/chemotherapy treatment of cancer. To further characterize the enzyme for possible use as a suicide gene, we constructed a replication-deficient retroviral vector that expressed either the wild-type enzyme that localizes to the cell nucleus or a mutant

(arg247ser) that localizes to the cytosol. A thymidine kinase-deficient osteosarcoma cell line was transduced with the recombinant virus and we compared the sensitivity and bystander cell killing when the cell lines were incubated with the pyrimidine nucleoside analogs (E)-5-(2-bromovinyl)-2'-deoxyuridine and 1-beta-D-arabinofuranosylthymine. In summary, we showed that the cells' sensitivity and the efficiency of bystander cell killing were not dependent on whether Dm-dNK was located in the nucleus or cytosol.

L24 ANSWER 15 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2001640683 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11691563
TITLE: Hamao Umezawa Memorial Award Lecture: "An Odyssey in the Viral Chemotherapy Field".
AUTHOR: De Clercq E
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium.. erik.declercq@rega.kuleuven.ac.be
SOURCE: International journal of antimicrobial agents, (2001 Oct) Vol. 18, No. 4, pp. 309-28.
Journal code: 9111860. ISSN: 0924-8579.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (LECTURES)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 7 Nov 2001
Last Updated on STN: 30 May 2002
Entered Medline: 29 May 2002
AB In the search of effective and selective chemotherapeutic agents for the treatment of viral infections, my "Odyssey" brought me to explore a variety of approaches, encompassing interferon and interferon inducers, suramin and other polyanionic substances, S-adenosylhomocysteine hydrolase inhibitors, inosine 5'-monophosphate dehydrogenase inhibitors, 5-substituted 2'-deoxyuridines such as (E)-5-(2-bromovinyl)-2'-deoxyuridine, acyclovir (esters) and other acyclic guanosine analogues, 2',3'-dideoxynucleoside analogues, non-nucleoside reverse transcriptase inhibitors (NNRTIs), bicyclams, and acyclic nucleoside phosphonates. This had led to the identification of a number of compounds, efficacious against such important viral pathogens as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), and other herpesviruses, pox-, adeno-, polyoma-, and papillomaviruses, and hemorrhagic fever viruses.

L24 ANSWER 16 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2001105972 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10993893
TITLE: Retroviral transduction of cancer cell lines with the gene encoding Drosophila melanogaster multisubstrate deoxyribonucleoside kinase.
AUTHOR: Zheng X; Johansson M; Karlsson A
CORPORATE SOURCE: Karolinska Institute, Division of Clinical Virology, Huddinge University Hospital, S-141 86 Stockholm, Sweden.
SOURCE: The Journal of biological chemistry, (2000 Dec 15) Vol. 275, No. 50, pp. 39125-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102

ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 8 Feb 2001

AB Nucleoside kinases from several species are investigated as "suicide genes" for treatment of malignant tumors by combined gene/chemotherapy. We have recently cloned a multisubstrate deoxyribonucleoside kinase of Drosophila melanogaster (Dm-dNK), and we have shown that the enzyme phosphorylates cytotoxic pyrimidine and purine nucleoside analogs. The broad substrate specificity of the enzyme, as well as its very high catalytic rate, makes it a unique member of the nucleoside kinase enzyme family. In the present study, we evaluated Dm-dNK as a suicide gene by constructing a replication-deficient retroviral vector that expresses the enzyme. The human pancreatic adenocarcinoma cell line MIA PaCa-2 and a thymidine kinase-deficient osteosarcoma cell line were transduced with the recombinant virus. We showed that Dm-dNK can be expressed in human cells, that the enzyme retained its enzymatic activity, and that it is localized in the cell nuclei due to a nuclear localization signal in its C-terminal region. The cells expressing Dm-dNK exhibited increased sensitivity to several cytotoxic nucleoside analogs, such as 1-beta-d-arabinofuranosylcytosine, 1-beta-d-arabinofuranosylthymine, (E)-5-(2-bromovinyl)-2'-deoxyuridine, 2-chloro-2'-deoxyadenosine, and 2',2'-difluorodeoxycytidine. These findings suggest that Dm-dNK may be used as a suicide gene in combined gene/chemotherapy of cancer.

L24 ANSWER 17 OF 24 MEDLINE on STN
ACCESSION NUMBER: 1998028690 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9359870
TITLE: Relaxed enantioselectivity of human mitochondrial thymidine kinase and chemotherapeutic uses of L-nucleoside analogues.
AUTHOR: Verri A; Priori G; Spadari S; Tondelli L; Focher F
CORPORATE SOURCE: Istituto di Genetica Biochimica ed Evoluzionistica, Consiglio Nazionale delle Ricerche, Pavia, Italy.
SOURCE: The Biochemical journal, (1997 Nov 15) Vol. 328 (Pt 1), pp. 317-20.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 22 Jan 1998
Last Updated on STN: 22 Jan 1998
Entered Medline: 8 Jan 1998

AB Our discovery that Herpes virus thymidine kinase (TK) and cellular deoxycytidine kinase lack enantioselectivity, being able to phosphorylate both D- and L-enantiomers of the substrate, suggested the use of unnatural L-nucleoside analogues as antiviral drugs (Herpes, hepatitis and immunodeficiency viruses). Several L-nucleoside analogues have displayed a short-term cytotoxicity much lower than their corresponding D-counterpart. Since the delayed cytotoxicity of a drug often depends on its effects on mitochondrial metabolism, we have investigated the degree of enantioselectivity of human mitochondrial thymidine kinase (mt-TK). We demonstrate that mt-TK does not show an absolute enantioselectivity, being able to recognize, although with lower efficiency, the L-enantiomers of thymidine, deoxycytidine and modified deoxyuridines, such as (E)-5-(2-bromovinyl)-2'-deoxyuridine and 5-iodo-2'-deoxyuridine. Interestingly, the reported negative co-operativity of mt-TK phosphorylating beta-D-2'-deoxythymidine (D-Thd), disappears when the deoxyribose moiety has the inverted configuration, resulting in the preferential phosphorylation of d-Thd even in the presence of high concentrations of the L-enantiomer. This, coupled with

the higher Km for beta-L-2'-deoxythymidine (L-Thd), makes mt-TK resistant to high concentrations of L-Thd and L-Thd analogues, minimizing the mitochondria-dependent delayed cytotoxicity that might be caused by the administration of L-nucleoside analogues as antivirals.

L24 ANSWER 18 OF 24 MEDLINE on STN
ACCESSION NUMBER: 94012339 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8407694
TITLE: Antivirals for the treatment of herpesvirus infections.
AUTHOR: De Clercq E
CORPORATE SOURCE: Rega Institute for Medical Research, K.U. Leuven, Belgium.
SOURCE: The Journal of antimicrobial chemotherapy, (1993 Jul) Vol. 32 Suppl A, pp. 121-32. Ref: 54
Journal code: 7513617. ISSN: 0305-7453.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 8 Nov 1993

AB Agents available to treat herpesvirus infections include idoxuridine, trifluridine, vidarabine and acyclovir for the topical treatment of herpetic eye infections; vidarabine and acyclovir for the systemic (intravenous) treatment of herpes encephalitis; acyclovir for the topical and systemic (oral) treatment of genital herpes; acyclovir for the systemic (intravenous, oral) treatment of HSV or varicella-zoster (VZV) infections in immunosuppressed patients; brivudin for the systemic (oral) treatment of HSV-1 or VZV infections in immunosuppressed patients; and ganciclovir and foscarnet for the systemic (intravenous) treatment of cytomegalovirus (CMV) retinitis in AIDS patients. Brivudin is also effective in the treatment of herpetic eye infections that no longer respond to idoxuridine, trifluridine, vidarabine or acyclovir; and foscarnet is effective in the treatment of infections with acyclovir-resistant, thymidine kinase-deficient (TK-) HSV or VZV mutants. Other antiviral agents considered for use in herpesvirus infections include brovavir, penciclovir (and its prodrug famciclovir), desciclovir (a prodrug of acyclovir), bishydroxymethylcyclobutylguanine (BHCG) and, in particular, 1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC). The latter is more active than either acyclovir or ganciclovir in the chemotherapy and prophylaxis of various HSV-1, HSV-2, TK- HSV, VZV or CMV infections in animal models.

L24 ANSWER 19 OF 24 MEDLINE on STN
ACCESSION NUMBER: 91113434 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2148885
TITLE: Effect of (E)-5-(2-bromovinyl)-2'-deoxyuridine on life-span and 5-fluorouracil metabolism in mice with hepatic metastases.
AUTHOR: Iigo M; Nishikata K; Nakajima Y; Hoshi A; De Clercq E
CORPORATE SOURCE: Chemotherapy Division, National Cancer Center Research Institute, Tokyo, Japan.
SOURCE: European journal of cancer (Oxford, England : 1990), (1990) Vol. 26, No. 10, pp. 1089-92.
Journal code: 9005373. ISSN: 0959-8049.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 29 Mar 1991

Last Updated on STN: 29 Jan 1996
Entered Medline: 6 Mar 1991

AB 5-Fluorouracil (5FU) is rapidly metabolised in the liver by dihydrouracil dehydrogenase. Bromovinyluracil is formed in the liver from (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) by pyrimidine nucleoside phosphorylase and is a potent inhibitor of dihydrouracil dehydrogenase. The co-administration of 5FU (intravenously) and BVDU (orally) was investigated in normal BDF1 mice and in those bearing liver metastases of Lewis lung carcinoma. 5FU alone rapidly disappeared from plasma and liver within 60 min of dosing. Administered with BVDU, 5FU persisted in plasma and liver for 60-180 min. The combination also significantly enhanced the life-span of tumour-bearing mice. 5FU plus BVDU may have therapeutic potential in the treatment of primary and secondary liver tumours.

L24 ANSWER 20 OF 24 MEDLINE on STN
ACCESSION NUMBER: 88194287 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3359416
TITLE: Combined effects of bromovinyldeoxyuridine and fractionated or continuous administration of 5-fluorouracil in P388 leukemia-bearing mice.
AUTHOR: Keizer H J; Pauwels R; Landuyt W; Balzarini J; van der Schueren E; De Clercq E
CORPORATE SOURCE: Department of Oncology, University Hospital St. Rafael, Katholieke Universiteit Leuven, Belgium.
SOURCE: Cancer letters, (1988 Mar) Vol. 39, No. 2, pp. 217-23. Journal code: 7600053. ISSN: 0304-3835.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198806
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 29 Jan 1996
Entered Medline: 2 Jun 1988

AB The combined effects of fractionated administration of the antiviral agent (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) and fractionated (4 injections at a 48-h interval) administration or continuous (7-day) infusion of 5-fluorouracil (FU) have been investigated in P388 leukemia-bearing mice. The LD50 of continuous FU infusion in normal mice was approximately 330 mg/kg, while that for the fractionated treatment was 160 mg/kg. When combined with BVDU (200 mumol/kg, 90 min before each FU injection; 4 injections at a 48-h interval), the LD50 of FU was decreased from 330 to 115 mg/kg and from 160 to 30 mg/kg, respectively. The 7-day continuous infusion of FU (up to a dose of 210 mg/kg) did not exert a therapeutic effect in P388-leukemic mice, and, similarly, combination of continuous FU infusion (at lower doses) with BVDU failed to increase the survival of the leukemic mice. If, however, FU was administered in fractionated doses, there was a dose-dependent increase in survival time of P388-leukemic mice, and simultaneous fractionated BVDU treatment allowed a 4-6-fold lower dose of FU to achieve the same increase in survival time, indicating that BVDU effectively increased the antitumor activity of FU in the leukemic mice.

L24 ANSWER 21 OF 24 MEDLINE on STN
ACCESSION NUMBER: 87100751 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3801279
TITLE: Enhancing effect of bromovinyldeoxyuridine on antitumour activity of 5-fluorouracil in mice bearing MOPC-315 plasmacytomas.
AUTHOR: Ben-Efraim S; Shoval S; de Clercq E
SOURCE: British journal of cancer, (1986 Nov) Vol. 54, No. 5, pp. 847-51.

Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198702
ENTRY DATE: Entered STN: 2 Mar 1990
Last Updated on STN: 2 Mar 1990
Entered Medline: 24 Feb 1987

L24 ANSWER 22 OF 24 MEDLINE on STN
ACCESSION NUMBER: 87072014 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3024419
TITLE: Towards a selective chemotherapy of virus infections. Development of bromovinyldeoxyuridine as a highly potent and selective antiherpetic drug.
AUTHOR: De Clercq E
SOURCE: Verhandelingen - Koninklijke Academie voor Geneeskunde van Belgie, (1986) Vol. 48, No. 4, pp. 261-90. Ref: 144
Journal code: 0413210. ISSN: 0302-6469.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198612
ENTRY DATE: Entered STN: 2 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 22 Dec 1986

L24 ANSWER 23 OF 24 MEDLINE on STN
ACCESSION NUMBER: 86203297 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3010086
TITLE: [Antiviral chemotherapy].
Antivirale Chemotherapie.
AUTHOR: Eggers H J
SOURCE: Monatsschrift Kinderheilkunde : Organ der Deutschen Gesellschaft fur Kinderheilkunde, (1986 Mar) Vol. 134, No. 3, pp. 122-9.
Journal code: 8206462. ISSN: 0026-9298.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
(ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198606
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 19 Jun 1986

AB After a discussion of the principles of antiviral chemotherapy, treatment and chemoprophylaxis of the following virus infections are reviewed in detail: the various manifestations of herpes simplex virus infections, varicella-zoster, cytomegalovirus infections, Epstein-Barr virus infections, laryngeal papillomas, and influenza A. Special reference is made to the treatment of immunocompromized patients. Acycloguanosine (acyclovir) has been found particularly useful in the treatment of herpes simplex virus and varicella zoster virus infections in immunocompromized patients and for herpesencephalitis. Varicella-zoster can also be treated effectively with bromovinyldeoxyuridine (BVDU). Toxicity of the currently used antiviral drugs is discussed as well as the problem of drug resistance.

L24 ANSWER 24 OF 24 MEDLINE on STN
ACCESSION NUMBER: 81169396 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6260876
TITLE: The sensitivity of acyclovir-resistant mutants of herpes simplex virus to other antiviral drugs.
AUTHOR: Field H; McMillan A; Darby G
SOURCE: The Journal of infectious diseases, (1981 Feb) Vol. 143, No. 2, pp. 281-5.
Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198106
ENTRY DATE: Entered STN: 16 Mar 1990
Last Updated on STN: 16 Mar 1990
Entered Medline: 13 Jun 1981

AB Three acyclovir (ACV)-resistant mutants derived from a strain of herpes simplex virus (HSV) type 1 were studied to determine the range of their resistance to nine drugs active against HSV. Two of the mutants were thymidine kinase-deficient (TK-) and were resistant to drugs that are usually phosphorylated by HSV TK. The other mutant induced normal levels of TK; it was of special interest since TK+ viruses appear more likely to multiply well in vivo. This mutant was inhibited by "TK-mediated" drugs: idoxuridine, which is already in use, and two drugs with promising clinical potential, 1-beta-arabinofuranosylthymine and E-5-(2-bromovinyl)-2'-deoxyuridine. All of the mutants were sensitive to trifluorothymidine and 9-beta-D-arabinofuranosyladenine. These results suggest that the study of cross-resistance of HSV strains in vitro will aid in the investigation of alternative drugs for use in effective chemotherapy.

L25 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:409543 CAPLUS
DOCUMENT NUMBER: 142:457053
TITLE: Human protein IAP (inhibitor of apoptosis protein) nucleobase oligomers, including dsRNA, shRNA, and siRNA, and their use for enhancing apoptosis in cancer therapy
INVENTOR(S): Lacasse, Eric; McManus, Daniel
PATENT ASSIGNEE(S): Aegera Therapeutics, Inc., Can.
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005042558	A1	20050512	WO 2004-CA1902		20041029
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2005148535	A1	20050707	US 2004-975974		20041028
CA 2542904	A1	20050512	CA 2004-2542904		20041029
EP 1682565	A1	20060726	EP 2004-789809		20041029
R: DE, FR, GB					
JP 2007510408	T	20070426	JP 2006-537024		20041029
PRIORITY APPLN. INFO.:			US 2003-516192P	P	20031030
			WO 2004-CA1902	W	20041029

AB The invention provides nucleobase oligomers and oligonucleotide duplexes that inhibit expression of an IAP (inhibitor of apoptosis protein), and methods for using them to induce apoptosis in a cell. Specifically, the invention provides nucleic acid sequences for siRNAs and shRNAs that target human XIAP, HIAP-1 or HIAP-2 genes. The nucleobase oligomers and oligomer complexes of the present invention may also be used to form pharmaceutical compns. The invention also features methods for enhancing apoptosis in a cell by administering a nucleobase oligomer or oligomer complex of the invention in combination with a chemotherapeutic or chemosensitizing agent. RNAi sequences and vectors producing shRNA (short hairpin RNA) were transfected into HeLa cells and evaluated for their effect on XIAP, cIAP-1, or cIAP-2 protein levels. XIAP protein could also be reduced by RNAi clones in transfected breast cancer cell line MDA-MB-231. In addition, cell survival was reduced in XIAP RNAi transfected breast cancer cell line after the transfected cells were treated with TRAIL (tumor necrosis factor-related apoptosis inducing ligand).

L25 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:409357 CAPLUS
DOCUMENT NUMBER: 142:457052
TITLE: Sequences of antisense IAP (inhibitor of apoptosis protein) oligomers and their use for treatment of proliferative diseases with a chemotherapeutic agent
INVENTOR(S): Lacasse, Eric; McManus, Daniel; Durkin, Jon P.

PATENT ASSIGNEE(S): Aegera Therapeutics, Inc., Can.
SOURCE: PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005042030	A1	20050512	WO 2004-CA1900	20041029
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005119217	A1	20050602	US 2004-975790	20041028
AU 2004284855	A1	20050512	AU 2004-284855	20041029
CA 2542884	A1	20050512	CA 2004-2542884	20041029
EP 1691842	A1	20060823	EP 2004-789807	20041029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004015779	A	20061226	BR 2004-15779	20041029
CN 1901939	A	20070124	CN 2004-80039601	20041029
JP 2007509861	T	20070419	JP 2006-537023	20041029
IN 2006MN00614	A	20070420	IN 2006-MN614	20060526
NO 2006002420	A	20060731	NO 2006-2420	20060529
PRIORITY APPLN. INFO.:			US 2003-516263P P	20031030
			WO 2004-CA1900 W	20041029

AB The invention claims the use of an antisense oligomer to human XIAP, IAP-1 or IAP-2 genes and a chemotherapeutic agent, and compns. and kits thereof, for the treatment of proliferative diseases. The invention further claims sequences for nucleobase oligomers that are antisense IAP (inhibitor of apoptosis protein) oligomers. The antisense IAP nucleobase oligomers specifically hybridize with polynucleotides encoding an IAP and reduce the amount of an IAP protein produced in a cell. Thus by reducing the IAP protein, the invention provides methods for inducing cancer cells to undergo apoptosis and for overriding anti-apoptotic signals in cancer cells. As an example of the invention, mice with s.c. H460 human lung carcinoma xenografts were injected intratumorally with XIAP antisense mixed-base 2'-O-Me RNA oligonucleotides (C5 and/or G4) and the drug vinorelbine. At the end of the 24 d treatment period, the mean relative tumor growth was reduced .apprx.70% in treated mice. The inhibition of tumor growth was correlated with down-regulation of human XIAP protein expression and an increased number of dead cells. The mice did not show any signs of cytotoxicity such as body weight loss.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

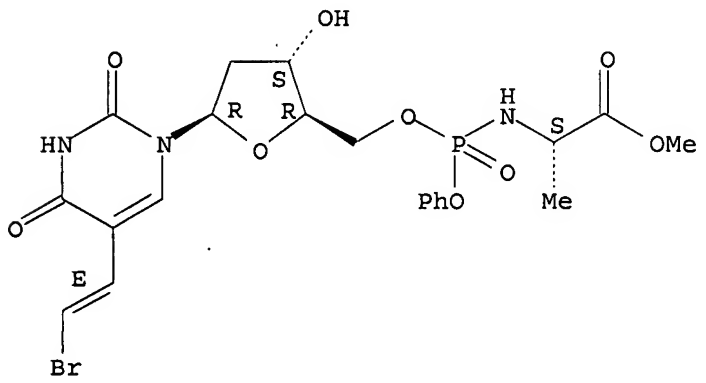
L33 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:694508 CAPLUS
DOCUMENT NUMBER: 138:248065
TITLE: Nucleoside transport inhibitors, dipyridamole and p-nitrobenzylthioinosine, selectively potentiate the antitumor activity of NB1011
AUTHOR(S): Boyer, Christopher R.; Karjian, Patricia L.; Wahl, Geoffrey M.; Pegram, Mark; Neuteboom, Saskia T. C.
CORPORATE SOURCE: NewBiotics, Inc, San Diego, CA, 92121, USA
SOURCE: Anti-Cancer Drugs (2002), 13(1), 29-36
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB NB1011, a novel anticancer agent, targets tumor cells expressing high levels of thymidylate synthase (TS). NB1011 is converted intracellularly to bromovinyldeoxyuridine monophosphate (BVdUMP) which competes with the natural substrate, deoxyuridine monophosphate, for binding to TS. Unlike inhibitors, NB1011 becomes a reversible substrate for TS catalysis. Thus, TS retains activity and converts BVdUMP into cytotoxic product(s). In vitro cytotoxicity studies demonstrate NB1011's preferential activity against tumor cells expressing elevated TS protein levels. Addnl., NB1011 has antitumor activity in vivo. To identify drugs which interact synergistically with NB1011, we screened 13 combinations of chemotherapeutic agents with NB1011 in human tumor and normal cells. Dipyridamole and p-nitrobenzylthioinosine (NBMPR), potent inhibitors of equilibrative nucleoside transport, synergized with NB1011 selectively against 5-fluorouracil (5-FU)-resistant H630R10 colon carcinoma cells [combination index (CI)=0.75 and 0.35] and Tomudex-resistant MCF7TDX breast carcinoma cells (CI=0.51 and 0.57), both TS overexpressing cell lines. These agents produced no synergy with NB1011 in Det551 and CCD18co normal cells (CI > 1.1) lacking TS overexpression. Dipyridamole potentiated NB1011's cytotoxicity in medium lacking nucleosides and bases, suggesting a non-salvage-dependent mechanism. We demonstrate that nucleoside transport inhibitors, dipyridamole and NBMPR, show promise for clin. efficacious combination with NB1011.

IT 232925-18-7, NB1011
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipyridamole and nitrobenzylthioinosine potentiate antitumor activity of NB1011)

RN 232925-18-7 CAPLUS
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:391469 CAPLUS
DOCUMENT NUMBER: 136:386347
TITLE: Preparation of synergistic enzyme catalyzed therapeutic activation (ECTA) nucleosides as antitumor agents
INVENTOR(S): Shepard, H. Michael; Boyer, Christopher
PATENT ASSIGNEE(S): Newbiotics, Inc., USA
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002039952	A2	20020523	WO 2001-US43566	20011116
WO 2002039952	A3	20021010		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002036455	A5	20020527	AU 2002-36455	20011116
US 2002147175	A1	20021010	US 2001-990799	20011116
PRIORITY APPLN. INFO.:			US 2000-249722P P	20001116
			WO 2001-US43566 W	20011116

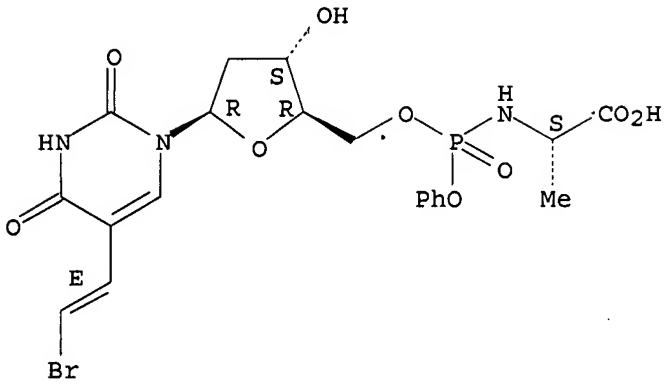
AB This invention provides compns. containing an effective amount of a novel substrate compound that selectively inhibit the proliferation of hyper-proliferative cells, for example, pathol. cells that endogenously over-express a target enzyme that confers resistance to biol. and chemo-therapeutic agents and an effective amount of a nucleoside transport antagonistic agents. Further provided by this invention is a method for treating a subject by delivering to the subject the composition as described herein. The compns. of this invention may be used alone or in combination with other chemo-therapeutics or alternative anti-cancer therapies such as radiation. Thus, (E)-5-(2-bromovinyl)-2'-deoxy-5'-uridyl Ph L-alaninylphosphoramidate (I) was prepared and tested in vitro human cells as synergistic antitumor agent. Vinblastine and doxorubicin showed potential synergy (CI < 1.1) with I in MCF7TDX and H630R10 cell. Irinotecan and taxol showed an additive or antagonistic interaction (CI = 1-1.4). The most antagonistic interaction was observed with 5-fluorouracil which gave CI = 3.19 in MCF7TDX cells. In light of these results, vinblastine and doxorubicin were chosen for further study.

IT 321982-16-5P 322454-65-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of synergistic enzyme catalyzed therapeutic activation nucleosides as antitumor agents)

RN 321982-16-5 CAPLUS
CN L-Alanine, N-[5-[(1E)-2-bromoethenyl]-2'-deoxy-P-phenyl-5'-uridylyl]-(9CI) (CA INDEX NAME)

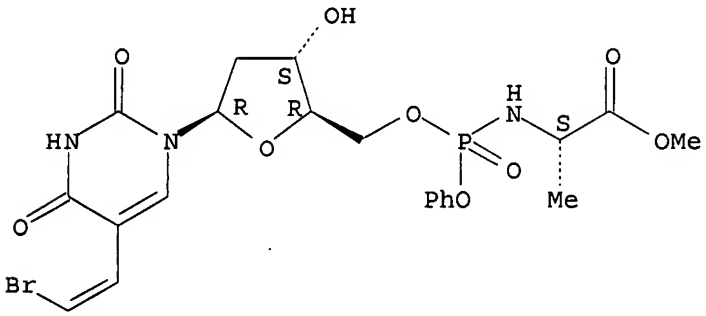
Absolute stereochemistry.

Double bond geometry as shown.



RN 322454-65-9 CAPLUS
CN L-Alanine, N-[5-(2-bromoethenyl)-2'-deoxy-P-phenyl-5'-uridylyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



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L4             STRUCTURE UPLOADED
L5           9 S L4 SSS SAM
L6         122 S L4 SSS FULL

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L7         979 S L3
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L10          0 S L7 AND CYTOSTATICS
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